REMARKS

Claims 1-50 are pending in the present application. By virtue of this response, claims 1, 10, 13, 22, 26, 35, 39, and 48 have been amended; and new claims 51-54 have been added. Support for new claims 51-54 is found in the specification, *inter alia*, on page 53, paragraph [0157]. The specification has been amended to correct sequence identifiers. Accordingly, no new matter has been added.

With respect to all claim amendments and cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Interview

Applicants thank Examiner Kimberly Ballard and Examiner's Supervisor Janet Andres for extending the courtesy for an interview on March 21, 2006, with Arnon Rosenthal, Carol Stratford, and Applicants' representative Jie Zhou, and for providing helpful suggestions, which are reflected in this response. Claims and references cited in the Office Action were discussed. The points presented by Applicants with respect to the rejections under 35 U.S.C. §102 and §103 are indicated in the Interview Summary and are reflected in this response. In addition, proposed amendments to claims reciting "delaying development of symptoms associated with Alzheimer's disease" were discussed. Applicants have amended claim 39 as suggested by the Examiners.

Claim Objections

The Examiner objects to claims 8, 9, 20, 21, 33, 34, 46, and 47 because SEQ ID NO:4 is a nucleic acid sequence according to the sequence listing submitted by Applicants on March 30, 2004, and claims recite "a monoclonal antibody comprising amino acid sequence of SEQ ID NO: 4 and 6." The Examiner states that it appears that the sequence ID numbers for SEQ ID NO:4 and 5 have been reversed in the sequence listing compared to the sequences listed no page 74 of the specification, and appropriate correction is required.

Applicants note that a new sequence listing is submitted with this response to correct this error. In view of this submission, Applicants respectfully request that this objection be withdrawn.

The Examiner further objects claims 1-50 because the claims recite a "pharmaceutical acceptable carrier". The Examiner states that a more grammatically correct phrase would recite "pharmaceutically acceptable carrier", and appropriate correction is required.

Applicants note that claims 1, 13, 26, and 39 have been amended to recite "pharmaceutically acceptable carrier". Applicants respectfully request that this objection be withdrawn.

Claim Rejections under 35 U.S.C. §112

Claims 39-50 are rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the specification, while being enabling for a method of reducing pathology associated with Alzheimer's disease in transgenic mice, does not reasonably provide enablement for a method of delaying development of a symptom associated with Alzheimer's disease as broadly claimed.

Applicants respectfully traverse the enablement rejection and submit the application teaches how to make and use the claimed invention. However, without acquiescence to the rejection, Applicants have amended claim 39 to recite "delaying development of a symptom associated with Alzheimer's disease in a subject having Alzheimer's disease" as suggested by the Examiners during the interview.

Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Nonstatutory Double Patenting Rejections

Claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 4, 7-17, 19, 28, 31-40, and 42 of copending App. No. 11/194,989.

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/194,989, at which time Applicants will address this issue.

Claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 3, 6-15, 17, 26, 29-38, and 40 of copending App. No. 11/195,207.

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/195,207, at which time Applicants will address this issue.

Claim Rejections under 35 U.S.C. §102

A. Claims 1, 2, 4, 6, 8-10, 13, 14, 16, 18, 20-22, 25-27, 29, 31, 33-35, 38-40, 42, 44, and 46-48 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bard et al. (Nat Med, August 2000, 6(8):916-919).

Applicants respectfully traverse this rejection, in view of the arguments presented below.

To anticipate a claim, a prior art reference must teach each and every element set forth in the claim. MPEP §2131. Furthermore, a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003), citing *Amgen, Inc. v. Hoechst Marion Rousses, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003).

The claims in the present application are directed to the use of an antibody that binds preferentially to amino acids 28-40 of A$\beta_{1\text{-}40}$ peptide for treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, or delaying development of a symptom associated with Alzheimer's disease in a subject having Alzheimer's disease.

Applicants respectfully submit that Bard et al. do not teach or suggest the claimed invention. Bard et al. state that antibody 21F12 was inactive in both *ex vivo* and *in vivo* assays in removing amyloid deposits and its inability to bind to plaques in unfixed brain sections explains its inability to trigger plaque clearance. See Table 1, and page 917, left col., line 16 to page 918, right col., line 7. Bard et al. further state that "[a]lthough 21F12 seemed to have relatively modest effect on plaque burden, there was no substantial reduction as determined by ELISA measurements (13,580 ng/g)." See page 916, left col., lines 4-7. U.S. Pat. No. 6,787,523, with Schenk (author) as an inventor, discloses that antibody 21F12 binds to A$\beta_{33\text{-}42}$. See col. 34, Table 6. Bard et al. also showed that antibody 16C11 failed to have any effect on plaque burden. See page 916, right col., lines 22-23; Table 1; and page 917, right col., line 16 to page 918, left col., line 7. This antibody is also reported to bind to A$\beta_{33\text{-}42}$. See page 93 of WO 00/72880 with Schenk (author) as an inventor, submitted in Information Disclosure Statement dated September 27, 2005. Since Bard et al. disclose that antibodies that bind to A$\beta_{33\text{-}42}$ are not useful in removing plaques in the animal model, Bard et al. do not teach or suggest the methods as claimed. This rejection may be properly withdrawn on this ground.

In addition, the disclosures in Bard et al. do not enable the claimed invention. As discussed above, Bard et al. disclose that antibodies that bind to A$\beta_{33\text{-}42}$ are not efficacious *in vivo* for removing plaques in the animal model, Bard et al. cannot be said to be an enabling reference for teaching the use of an antibody as claimed for treating Alzheimer's disease. This rejection may be properly withdrawn on this ground.

Applicants also respectfully note that binding of an antibody to $\underline{\text{A}\beta_{33\text{-}42}}$ does not necessarily suggest that this antibody preferentially binds to amino acids 28-40 of $\underline{\text{A}\beta_{1\text{-}40}}$. For example, if binding of the antibody depends on the last two amino acids on the C-terminus of $\underline{\text{A}\beta_{33\text{-}}}$

$_{42}$, this antibody may not bind to Aβ_{1-40} because those two amino acids are not present on the C-terminus of Aβ_{1-40}. Thus, antibody 21F12 may not necessarily meet the binding specificities recited in claims 1, 2, 4, 6, 8, 9, 13, 14, 16, 18, 20, 21, 26, 27, 29, 31, 33, 34, 39, 40, 42, 44, 46, and 47.

In view of the above, Applicants respectfully submit that Bard et al. do not teach or suggest the claimed invention. Further as discussed above, the disclosure in Bard et al. cannot be said to enable Applicants' claimed invention.

Accordingly, Bard et al. do not anticipate claims 1, 2, 4, 6, 8-10, 13, 14, 16, 18, 20-22, 25-27, 29, 31, 33-35, 38-40, 42, 44, and 46-48. Withdrawal of this rejection is therefore respectfully requested.

B. Claims 1, 2, 8-14, 20-27, 33-40, and 46-50 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Pat. No. 6,787,523 (Schenk). The Examiner states that Schenk teaches the therapeutic use of an anti-Aβ antibody in the prevention or treatment of Alzheimer's disease, and such antibodies can be monoclonal, humanized, or human antibodies to Aβ. The Examiner further states that characteristics of antibody 21F12 meets the limitations in claims 1, 2, 8, 9, 13, 14, 20, 21, 26, 27, 33, 34, 39, 40, 46, and 47. The Examiner alleges that Schenk anticipates claims 1, 2, 8-14, 20-27, 33-40, and 46-50.

Applicants respectfully traverse this rejection.

As provided above, to anticipate a claim, a prior art reference must teach each and every element set forth in the claim. MPEP §2131. Furthermore, a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003), citing *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003).

The claims pending in the present application are directed to the use of an antibody that binds preferentially to amino acids 28-40 of Aβ_{1-40} peptide to treat Alzheimer's disease, suppress formation of amyloid plaques, reduce amyloid plaques, or delay development of a symptom associated with Alzheimer's disease in subject having Alzheimer's disease.

Applicants respectfully submit that the disclosures in Schenk do not teach or suggest the claimed invention. Schenk provides a prophetic example for administering anti-Aβ antibodies, such as 21F12, to PDAPP mice over a 4 month period, and performing post mortem analysis of Aβ levels and toxicology. Further experimental evidence from his group clearly showed that this antibody was ineffective to treat Alzheimer's disease, suppress formation of amyloid plaques, reduce amyloid plaques, or delay development of a symptom associated with Alzheimer's disease in subject having Alzheimer's disease. For example, a related PCT application publication WO 00/72880 (published December 7, 2000, by Schenk et al; provided in Applicants' Information Disclosure Statement) discloses that antibody 21F12 did not show significant treatment effects in the animal model. See, e.g., pages 83-93, and Tables 13-15. WO 00/72880 further states that it has been found that certain antibodies to epitopes within residues 33-42 of Aβ lack activity. See page 19, lines 1-3. In addition, as discussed above, Bard et al. disclose antibodies that bind to $A\beta_{33\text{-}42}$ lack *in vivo* efficacy. Thus, in view of WO 00/72880 and Bard et al., U.S. Pat. No. 6,787,523 does not teach or suggest use of antibodies as claimed for treating Alzheimer's disease. This rejection may be properly withdrawn on this ground.

Since WO 00/72880 and Bard et al. disclose that antibodies directed to epitopes within residues 33-42 lack activity, U.S. Pat. No. 6,787,523 is not an enabling reference for use of an antibody as claimed in treating Alzheimer's disease. This rejection may be properly withdrawn on this ground.

In addition, as discussed above, antibody 21F12 may not necessarily meet the binding specificities recited in the claims.

Accordingly, Applicants respectfully submit that this reference does not anticipate claims 1, 2, 8-14, 20-27, 33-40, and 46-50. Withdrawal of this rejection under 35 U.S.C. §102(e) is therefore respectfully requested.

Claim Rejections under 35 U.S.C. §103

Claims 1, 2, 4-14, 16-27, 29-40, and 42-50 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bard et al. (Nat. Med., August 2000, 6(8):916-919) in view of Zeitlin et al. (Microbes and Infection, 2000, 2:701-708). The Examiner states that Bard et al. teach the use of peripherally administered anti-Aβ antibodies to reduce pathology in PDAPP transgenic mice as set forth *supra*; however, Bard et al. do not teach lower antibodies affinities for this monoclonal antibody (such as 1 nM or less) or humanized or human antibodies. The Examiner further states that Zeitlin et al. teach or suggest monoclonal antibodies, antibodies with improved affinities, humanized antibodies, and fully human antibodies may allow antibodies achieve better clinical benefit. It is the Examiner's position that it would have been obvious to the persons of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the methods of reducing amyloid burden in a Alzheimer's disease model using the monoclonal antibody 21F12 as taught by Bard et al. with selecting for a high affinity monoclonal and humanized or human monoclonal antibodies as taught by Zeitlin et al. to create high affinity anti-Aβ antibodies or humanized or human anti-Aβ antibodies for the treatment of Alzheimer's disease. The Examiner further alleges that one of skill in the art would have been motivated to make these modifications and would have an expectation of success in treating Alzheimer's disease because Bard et al. teach that it would be expected to work (entire document).

Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The claims pending in the present application are directed to the use of an antibody that binds preferentially to amino acids 28-40 of Aβ_{1-40} peptide to treat Alzheimer's disease, suppress formation of amyloid plaques, reduce amyloid plaques, or delay development of a symptom associated with Alzheimer's disease in subject having Alzheimer's disease.

Applicants submit that the cited references, even if combined, do not teach or suggest all of the claimed limitations. As discussed in the above section, Bard et al. do not teach or suggest methods for treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, or delaying development of a symptom associated with Alzheimer's disease in subject having Alzheimer's disease by administering an antibody that binds preferentially to amino acids 28-40 of Aβ_{1-40} peptide. The above discussion applies equally here. Zeitlin et al. do not cure this deficiency of Bard et al. Zeitlin et al. do not teach or suggest using an anti-Aβ antibody for treating Alzheimer's disease. Instead, Zeitlin et al. describe attributes of a variety of antibodies that are potentially useful in therapeutic indications, focusing on infectious disease. Since Bard et al. and Zeitlin et al., even if combined, do not teach or suggest all of the claim limitations, the Examiner has not set forth a *prima facie* case for obviousness. Thus, the obviousness rejection may be properly withdrawn on this ground.

To establish a *prima facie* case of obviousness, there must also be a reasonable expectation of success. As discussed above, Bard et al. disclose that both antibody 21F12 and antibody 16C11, which bind to Aβ_{33-42}, lack *in vivo* efficacy in removing plaques in the animal model. Bard et al. provide no suggestion or basis for one skilled in the art to expect that antibodies having *in vivo* efficacy can be generated by improving the affinity of these antibodies, humanizing these antibodies, or making a human antibody to the same epitope. Zeitlin et al. teach some of the unique qualities of monoclonal antibodies in treating or preventing infectious diseases, which are quite different from Alzheimer's disease. Based on the above, it would not have been obvious for one of ordinary skill in the art to combine the teachings of these two references with a reasonable expectation of success in removing plaques and treating Alzheimer's disease using antibodies that bind to C-terminal amino acid residues of an Aβ peptide. On this ground, the obviousness rejection may be properly withdrawn.

Furthermore, Bard et al. teach away from the concept of using antibodies directed to C-terminal amino acid residues of an Aβ peptide to clear amyloid plaques. Bard et al. state that by comparison of six different antibodies tested, antibodies 10D5, 3D6 and pabAβ1-42 were all active the *ex vivo* assay and demonstrated efficacy *in vivo*; in contrast, 16C11, 21F12 and the control antibody TM2a were inactive in both assays. See, page 917, right col., line 16 to page 918, left col., line 1. Antibodies 3D6 and 10D5 have reported to bind to amino acid residues 1-5 and 3-6, respectively. See WO 00/72880, page 97, Table 16. Antibody pabA$\beta_{1\text{-}42}$ is a polyclonal antibody obtained from mice immunized with A$\beta_{1\text{-}42}$. See Bard et al., left col., lines 33-35. Since Bard et al. teach that antibodies that bind to A$\beta_{33\text{-}42}$ do not have *in vivo* efficacy to clearing plaques, a person of ordinary skill would be discouraged from developing antibodies directed to C-terminal residues of an Aβ peptide for therapeutic use in Alzheimer's disease. Thus, one skilled in the art would not have been motivated to make and use these antibodies and have a reasonable expectation of success.

In view of the above, the Examiner has not set forth a *prima facie* case for obviousness for claims 1, 2, 4-14, 16-27, 29-40, and 42-50. Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 514712001500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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